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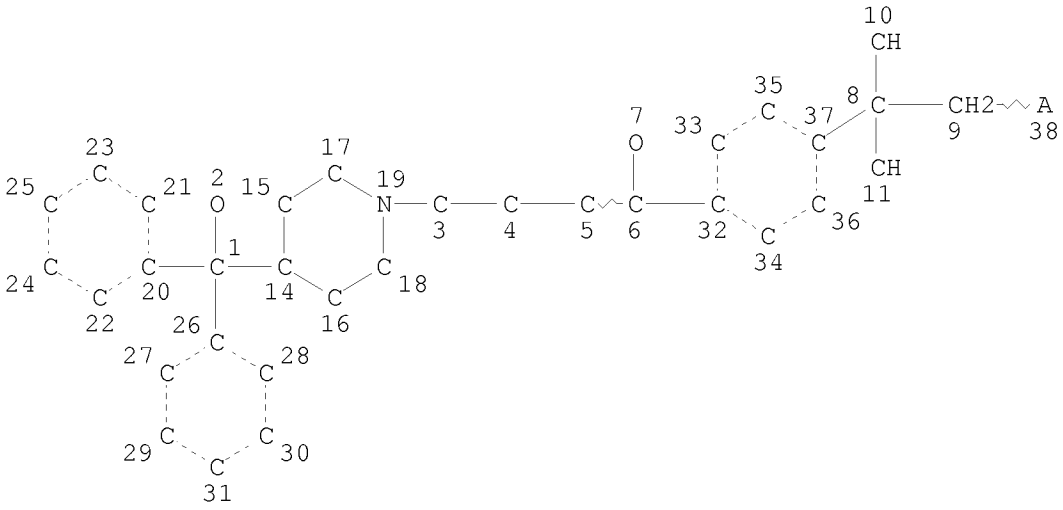
L10 STR



NODE ATTRIBUTES:
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 36

STEREO ATTRIBUTES: NONE

=> d his l11

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=> d bib abs l112 1-25
L112 NOT FOUND
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has been deleted. To see the L-numbers currently defined in this
session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> d bib abs l12 1-25

L12 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:1118903 CAPLUS
DN 148:77147
TI Oxidation of terfenadine by Streptomyces platensis: Influence of culture medium on metabolite formation
AU Mazier, Claire; Lombard, Murielle; Sari, Marie-Agnes; Buisson, Didier
CS Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 CNRS, Universite Rene Descartes-Paris V, Paris, 75270, Fr.
SO Biocatalysis and Biotransformation (2007), 25(5), 401-407
CODEN: BOBOEQ; ISSN: 1024-2422
PB Informa Healthcare
DT Journal
LA English
AB The biotransformation of terfenadine into a primary alc.,

hydroxyterfenadine, followed by its oxidation to an acid, fexofenadine, was investigated using Streptomyces platensis cells. Time-courses of metabolite formation were established, and the results underlined the modulation of the alc. to acid formation ratio according to culture conditions. Optimization of the hydroxylation step (pH, temperature, culture medium composition) led to the preparation of hydroxyterfenadine with a good yield
(51%) using cells grown in culture medium without soybean peptone. In contrast, when incubations were performed with cells cultured in a medium containing soybean peptone, the alc. to acid formation ratio decreased. The efficiency of the conversion to fexofenadine was shown to depend on the age of the cells, thus suggesting the induction of an oxidative activity. Both the hydroxylation reaction and the following two-oxidation steps leading to the acid seemed to depend on oxygen.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:791990 CAPLUS
DN 142:5516
TI Microbial oxidation of terfenadine and ebastine into fexofenadine and carebastine
AU Mazier, Claire; Jaouen, Maryse; Sari, Marie-Agnes; Buisson, Didier
CS Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, URA 400 CNRS, Universite Rene Descartes Paris V, Paris, 75270, Fr.
SO Bioorganic & Medicinal Chemistry Letters (2004), 14(21), 5423-5426
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier B.V.
DT Journal
LA English
OS CASREACT 142:5516
AB The oxidation of tert-butyl-Ph group of the title compds. by some microorganisms was studied. We have optimized the conditions of culture to increase the formation of acid metabolites and to avoid the formation of side products. We showed that an oxidative activity is induced by soybean peptones in Streptomyces platensis. The biol. active compds., fexofenadine and carebastine, are produced in good yield (86-95%) by Absidia corymbifera.
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:527345 CAPLUS
DN 142:190206
TI Lead identification for modulators of multidrug resistance based on in silico screening with a pharmacophoric feature model
AU Langer, Thierry; Eder, Monika; Hoffmann, Remy D.; Chiba, Peter; Ecker, Gerhard F.
CS Institute of Pharmacy, University of Innsbruck, Innsbruck, Austria
SO Archiv der Pharmazie (Weinheim, Germany) (2004), 337(6), 317-327
CODEN: ARPMAS; ISSN: 0365-6233
PB Wiley-VCH Verlag GmbH & Co. KGaA
DT Journal
LA English
AB Considerable effort has been devoted to the characterization of P-glycoprotein - drug interaction in the past. Systematic quant. structure-activity relationship (QSAR) studies identified both predictive physicochem. parameters and pharmacophoric substructures within homologous series of compds. Comparative mol. field anal. (CoMFA) led to distinct 3D-QSAR models for propafenone and phenothiazine analogs. Recently, several pharmacophore models have been generated for diverse sets of

ligands. Starting from a training set of 15 propafenone-type MDR-modulators, we established a chemical function-based pharmacophore model. The pharmacophoric features identified by this model were (i) one hydrogen bond acceptor, (ii) one hydrophobic area, (iii) two aromatic hydrophobic areas, and (iv) one pos. ionizable group. In silico screening of the Derwent World Drug Index using the model led to identification of 28 compds. Substances retrieved by database screening are diverse in structure and include dihydropyridines, chloroquine analogs, phenothiazines, and terfenadine. On the basis of its general applicability, the presented 3D-QSAR model allows in silico screening of virtual compound libraries to identify new potential lead compds.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:428909 CAPLUS
DN 141:7026
TI Method for the preparation of terfenadine and its derivatives
IN Veverka, Miroslav; Bohac, Andrej; Kriz, Miroslav; Varga, Ivan
PA Zentiva, A.S., Slovakia
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004043922	A1	20040527	WO 2003-SK21	20031107
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	SK 285548	B6	20070301	SK 2002-1623	20021113
	AU 2003301983	A1	20040603	AU 2003-301983	20031107
PRAI	SK 2002-1623	A	20021113		
	WO 2003-SK21	W	20031107		

OS MARPAT 141:7026
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Terfenadine and its derivs. [I; R1 = Me, Et, (un)protected hydroxymethyl, (un)protected carboxy; R2 = hydrogen, OH-protecting group] is prepared in high yield and selectivity by the reaction of a benzaldehyde derivative (II; X1 = CHO) with the Grignard reagent XMgO(CH2)3MgX2 (X, X2 = Br, Cl) to give the benzyl alc. derivative (III) which is reacted in the presence of CH3SO3H, 4-H3CC6H4SO3H, or benzenesulfonyl chloride with the piperidine derivative (IV; R1, R2 = hydrogen, Me, hydroxy, methoxy, double bond) to give I.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:599497 CAPLUS
DN 140:86971
TI Substrate dependent inhibition profiles of fourteen drugs on CYP3A4 activity measured by a high throughput LCMS/MS method with four probe drugs, midazolam, testosterone, nifedipine and terfenadine
AU Racha, Jagdish K.; Zhao, Z. Sylvia; Olejnik, Nicholas; Warner, Nadine; Chan, Rebecca; Moore, David; Satoh, Hiroko
CS Non-Clinical Drug Safety Department, Hoffmann-La Roche Inc., Nutley, NJ, USA
SO Drug Metabolism and Pharmacokinetics (2003), 18(2), 128-138
CODEN: DMPRB8; ISSN: 1347-4367
PB Japanese Society for the Study of Xenobiotics
DT Journal
LA English
AB The CYP3A4 enzyme is known for its atypical inhibition kinetics; ligand inhibition can differ depending upon the probe drug used. A high throughput-LCMS/MS CYP3A4 inhibition assay with four substrate drugs was developed to minimize the potential oversight of CYP3A4 inhibition. The assay uses a 96-well format, human liver microsomes, and four CYP3A4 substrate drugs, midazolam, testosterone, nifedipine and terfenadine. After incubation of the individual substrate with human liver microsomes, the reaction is stopped by solid phase extraction and the four probe metabolites produced are pooled and measured by LCMS/MS with multiple-ion-monitoring mode. Using this assay, the IC50 values of fourteen compds. recognized as substrates/inhibitors of CYP3A4, were measured for the CYP3A4 catalyzed-metabolism of probe drugs. IC50 values were also obtained for the common set of compds. by the microtiter plate fluorescent assays with cDNA-expressed CYP3A4. Comparison of the results from the two methods suggests that decision making should be cautiously executed to predict drug interaction potential caused by inhibition of CYP3A4 considering the gap between the two assays and various other factors.
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:61498 CAPLUS
DN 139:110986
TI Performance of an ultra-low elution-volume 96-well plate: drug discovery and development applications
AU Mallet, Claude R.; Lu, Ziling; Fisk, Ray; Mazzeo, Jeffrey R.; Neue, Uwe D.
CS Waters Corporation, Milford, MA, 01757-3696, USA
SO Rapid Communications in Mass Spectrometry (2003), 17(2), 163-170
CODEN: RCMSEF; ISSN: 0951-4198
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Recently, sample preparation has been considered to be the major cause of bottlenecks during high-throughput anal. With the assistance of robotic liquid handlers and the 96-well plate format, more samples can be prepared for subsequent liquid chromatog./tandem mass spectrometry (LC/MS/MS) anal. Protein precipitation is still widely used despite potential loss of sensitivity or variable results due to ion suppression. The use of solid-phase extraction (SPE) clearly gives superior results but may not be as cost effective as protein precipitation due to the labor and material costs associated with the process. Here, a novel 96-well SPE plate is described that was designed to minimize the elution volume required for quant. elution of analytes. The plate is packed with 2 mg of a high-capacity SPE sorbent that allows loading of up to 750 μL of plasma, while the novel design permits

elution with as little as 25 μL. Therefore, the plate offers up to a 15-fold increase in sample concentration The evaporation and reconstitution step that is typically required in SPE is avoided due to the concentrating ability of the plate. Examples of applications in drug discovery/development are shown and results are compared to protein precipitation Excellent sensitivity and linearity are demonstrated.

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:970095 CAPLUS
DN 139:30082
TI Receptor-dependent regulation of the CYP3A4 gene
AU Gibson, G. Gordon; El-Sankary, Wafaa; Plant, Nick J.
CS School of BioMedical and Life Sciences, Molecular Toxicology Group, University of Surrey, Guildford, Surrey, GU2 5XH, UK
SO Toxicology (2002), 181-182, 199-202
CODEN: TXCYAC; ISSN: 0300-483X
PB Elsevier Science Ltd.
DT Journal
LA English
AB A CYP3A4 promoter-reporter gene construct has been used to assess the ability of 16 known (in vivo) and putative (in vitro) inducers to transactivate a CYP3A4 reporter gene in HepG2 cells. With the exception of pravastatin, the remaining 15 compds. transactivated the CYP3A4 reporter gene with differing inductive abilities (Imax:EC50) over two orders of magnitude, ranging from 1.1 (phenytoin) to 222.9 (lovastatin) in a receptor-supplemented system and it is proposed that the lack of response to pravastatin is due to loss of the known hepatic uptake transporter in HepG2 cells. In addition, reporter gene assays were used to investigate two promoter mutants namely a T to C change at -191 bp in the hepatic nuclear factor 3 binding site (HNF-3, -187 to -194 bp) and an A to G change at -205 bp in the estrogen response element (ERE, -202 to -212 bp), which conferred differential responsiveness to steroid and xenobiotic inducers.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:408068 CAPLUS
DN 135:19556
TI Preparation of [(piperidinoalkanoyl)phenyl]propionates and analogs as antihistaminics
IN Krauss, Richard C.; Strom, Robert M.; Scortichini, Carey L.; Kruper, William J.; Wolf, Richard A.; Wu, Weishi W.; Carr, Albert A.; Hay, David A.; Rudisill, Duane E.; Panzone, Gianbattista
PA Merrell Pharmaceuticals Inc., USA
SO U.S., 60 pp., Cont.-in-part of U.S. Ser. No. 237,466.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6242606	B1	20010605	US 1994-275685	19940714
	CA 2166059	A1	19950105	CA 1994-2166059	19940526
	CA 2166059	C	20050816		
	CA 2362337	C	19950105	CA 1994-2362337	19940526
	CA 2362337	A1	19950105		
	CA 2362339	C	19950105	CA 1994-2362339	19940526

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     CA 2362339           A1    19950105
     CN 1128987           A     19960814    CN 1994-193031         19940526
     EP 1260504           A1    20021127    EP 2002-12626          19940526
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE
     ES 2190442           T3    20030801    ES 1994-919264         19940526
     CN 1603291           A     20050406    CN 2004-10058716       19940526
     CN 1275916           C     20060920
     EP 1953142           A1    20080806    EP 2008-8300           19940526
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     ZA 9404380           A     19950209    ZA 1994-4380           19940620
     IL 110086            A     20010913    IL 1994-110086         19940622
     IL 143607            A     20050725    IL 1994-143607         19940622
     IL 143613            A     20050725    IL 1994-143613         19940622
     IL 143619            A     20050831    IL 1994-143619         19940622
     US 6147216           A     20001114    US 1995-458747         19950602
     AU 9915458           A     19990624    AU 1999-15458          19990208
     AU 734870            B2    20010621
     CN 1274711           A     20001129    CN 2000-101035         20000112
     US 20010018521       A1    20010830    US 2000-725291         20001129
     US 6566526           B2    20030520
     US 20010020114       A1    20010906    US 2000-725259         20001129
     US 6552200           B2    20030422
     US 6340761           B1    20020122    US 2000-725298         20001129
     US 20010000038       A1    20010315    US 2000-726625         20001201
     US 6479663           B2    20021112
     US 20020198407       A1    20021226    US 2000-726580         20001201
     US 6555689           B2    20030429
     US 20020007085       A1    20020117    US 2000-729203         20001205
     US 6548675           B2    20030415
     US 20010021791       A1    20010913    US 2000-731654         20001208
     US 6559312           B2    20030506
     US 20020077482       A1    20020620    US 2001-818966         20010328
     US 6441179           B2    20020827
     US 20010031895       A1    20011018    US 2001-824788         20010404
     US 6348597           B2    20020219
     HK 1032226           A1    20041231    HK 2001-102808         20010420
     MX 2001PA07687       A     20030303    MX 2001-PA7687         20010730
     MX 2001PA07688       A     20030303    MX 2001-PA7688         20010730
     MX 2001PA07692       A     20030303    MX 2001-PA7692         20010730
     MX 2001PA07693       A     20030303    MX 2001-PA7693         20010730
     US 20030220496       A1    20031127    US 2003-364641         20030212
     US 6777555           B2    20040817
     JP 2005320329        A     20051117    JP 2005-133801         20050502
     HK 1075884           A1    20070511    HK 2005-107826         20050907
PRAI US 1993-82693        B2    19930625
     US 1993-144084       A2    19931027
     US 1994-237466       A2    19940511
     AU 1994-70466        A3    19940526
     CA 1994-2166059      A3    19940526
     EP 1994-919264       A3    19940526
     EP 2002-12626        A3    19940526
     JP 1995-502831       A3    19940526
     IL 1994-110086       A     19940622
     US 1994-275685       A1    19940714
     US 2000-725259       A3    20001129
OS   MARPAT 135:19556
GI
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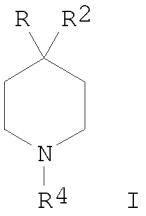

I

AB Title compds. [I; R = R1CPh2Om; R1 = H or OH; R2 = H; R1R2 = bond; R4 = (CH2)nZZ1CMe2R3; R3 = CO2H or alkoxycarbonyl; Z = CO or CH(OH); Z1 = (2-hydroxy) 1,4-phenylene; m = 0 or 1; N = 1-5] were prepared as antihistaminics (no data). Thus, PhCMe2CO2Me was acylated by Cl(CH2)3COCl and the product aminated by α,α-diphenyl-4-piperidinemethanol to give I.HCl [R = HOCPh2, R2 = H, R4 = (CH2)3COC6H4(CMe2CO2Me)-4].
RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:706359 CAPLUS
DN 133:280646
TI Procedure for the biocatalyzed regioselective oxidation of terfenadine
IN Schmitz, Guenther; Takors, Rald; Weuster-Botz, Dirk; Wandrey, Christian
PA Forschungszentrum Julich G.m.b.H., Germany
SO Ger. Offen., 10 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19913862	A1	20001005	DE 1999-19913862	19990326
	DE 19913862	C2	20030410		
PRAI	DE 1999-19913862		19990326		

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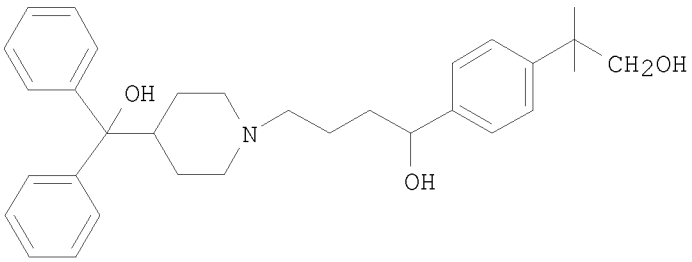


I

AB A process is provided for the biocatalytic conversion and separation of a racemic compound that has low water solubility in a membrane coupled bioreactor.
In this process the substrate compound which is in microcryst. form and the biocatalyst are retained in the bioreactor while the product is removed via crossflow filtration. Thus terfenadine was biocatalyzed by Cunninghamella blakesleeana to an alc.(I) in a membrane coupled stirred

tank fermentor. The alc. I was then removed from the fermentor through coupled crossflow filter membrane while the microbial cells and microcryst. terfenadine were retained. After eighty hours of fermentation, the concentration of I rose to ~ 200 mg/l and removed at this level for the remaining 120 h of fermentation A total of 900 mg/l of I was produced over the course of the fermentation The alc. produced, I, was recovered from the permeate by ion exchange chromatog. Also in the scope of the invention is the conversion of I to the carboxylic acid fexofenadine which is facilitated by the activation of the tert-Bu group of terfenadine to an alc. by the regioselective oxidation

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:505927 CAPLUS
DN 133:334093
TI Regioselective oxidation of terfenadine with Cunninghamella blakesleeana
AU Schmitz, G.; Franke, D.; Stevens, S.; Takors, R.; Weuster-Botz, D.; Wandrey, C.
CS Institute of Biotechnology, Research Centre Juelich, Julich, D-52428, Germany
SO Journal of Molecular Catalysis B: Enzymatic (2000), 10(1-3), 313-324
CODEN: JMCEF8; ISSN: 1381-1177
PB Elsevier Science B.V.
DT Journal
LA English
OS CASREACT 133:334093
AB The regioselective oxidation of terfenadine with the fungi Cunninghamella blakesleeana was studied as a biochem. alternative for the chemical synthesis of the antihistaminic drug fexofenadine. It was demonstrated that C. blakesleeana oxidizes the tert-Bu group of terfenadine to the corresponding alc. 1-[4-(1,1-dimethyl-2-hydroxyethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanol. A continuous process for regioselective oxidation of terfenadine was developed. Terfenadine was supplied micro-crystalline due to the low solubility in water. Optimum reaction conditions with respect to medium composition, temperature, pH, pO2, co-substrate and feeding rates were found by means of reaction engineering studies. A cross-flow microfiltration unit was operated in a bypass of a lab-scale stirred tank reactor for retention of the biocatalysts and the micro-crystalline substrate. The alc. was continuously removed with the filtrate to minimize product inhibition. Continuous biotransformation of micro-crystalline terfenadine with C. blakesleeana in the membrane reactor system with a dilution rate of 33 h at co-substrate concns. of about 1 up to 3 g/l glycerol in the reactor resulted in a space-time yield of 145 mg of alc./l/day and an alc. yield of 71%. The produced alc. was easily isolated from the filtrate by adsorption on XAD-4 resin followed by elution with methanol (concentration factor 7).

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:303921 CAPLUS
DN 133:114514
TI Analysis of hydroxylated and N-dealkylated metabolites of terfenadine in microsomal incubates by liquid chromatography-mass spectrometry
AU Madani, S.; Howald, W. N.; Lawrence, R. F.; Shen, D. D.
CS Department of Pharmaceutics, University of Washington, Seattle, WA, USA
SO Journal of Chromatography, B: Biomedical Sciences and Applications (2000),

741(2), 145-153
CODEN: JCBBEP; ISSN: 0378-4347
PB Elsevier Science B.V.
DT Journal
LA English
AB This report describes an assay for the H1-receptor antagonist, terfenadine, and its two primary metabolites, terfenadine alc. (TOH) and azacyclonol (AZ), using pos.-ion, electrospray ionization-liquid chromatog.-mass spectrometry. The assay was developed in support of kinetic studies of terfenadine oxidative metabolism in human liver and intestinal microsomes, which required quantification of incubate metabolites at low nanomolar concns. Terfenadine metabolites were extracted from basified microsomal incubates into methylene chloride. Reconstituted exts. were subject to liquid chromatog. separation on a cyano-reverse phase column. The [M+H]+ ions of terfenadine, terfenadine metabolites, and internal standard were monitored in the effluent by quadrupole mass spectrometry. The assay demonstrated linearity over an incubate concentration range of 5-250 and 12.5-1250 ng/mL for the metabolites and the parent drug, resp. The resp. limits of detection and quantitation for all three analytes were 1.5 and 5 ng/mL of microsomal incubate. Replicate anal. of quality control samples exhibited intra-day coeffs. of variation ranging from 3.3% to 7.8% for the three analytes. The corresponding inter-day coeffs. of variation ranged from 4.2% to 8.6%. The reproducibility and sensitivity of the assay, combined with the selectivity of mass spectrometric detection, should allow an accurate kinetic characterization of terfenadine oxidation mediated by the high affinity CYP3A enzymes in human liver and intestinal microsomes.
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1999:614162 CAPLUS
DN 131:213195
TI Novel method for preparing fexofenadine
IN Azerad, Robert; Biton, Jacques; Lacroix, Isabelle
PA Hoechst Marion Roussel, Fr.
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9947693	A1	19990923	WO 1999-FR625	19990318
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2776302	A1	19990924	FR 1998-3349	19980319
FR 2776302	B1	20020412		
AU 9928427	A	19991011	AU 1999-28427	19990318
EP 1062358	A1	20001227	EP 1999-909036	19990318
EP 1062358	B1	20030604		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002506653	T	20020305	JP 2000-536876	19990318
AT 242333	T	20030615	AT 1999-909036	19990318
PT 1062358	T	20031031	PT 1999-909036	19990318
ES 2196783	T3	20031216	ES 1999-909036	19990318

	US 6558931	B1	20030506	US 2000-646517	20001031
	US 20060019358	A1	20060126	US 2003-392699	20030320
	US 7241601	B2	20070710		
PRAI	FR 1998-3349	A	19980319		
	WO 1999-FR625	W	19990318		
	US 2000-646517	A3	20001031		

AB The invention concerns a method for preparing fexofenadine from terfenadine by a bioconversion process using Absidia corymbifera LCP 63-1800 or Streptomyces platensis NRRL 2364 strain.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1999:328140 CAPLUS
DN 131:110864
TI Interplay between CYP3A-mediated metabolism and polarized efflux of terfenadine and its metabolites in intestinal epithelial Caco-2 (TC7) cell monolayers
AU Raeissi, Shamsi D.; Hidalgo, Ismael J.; Segura-Aguilar, Juan; Artursson, Per
CS Drug Metabolism and Pharmacokinetics, Rhone-Poulenc Rorer Central Research, Collegeville, PA, 19426-0107, USA
SO Pharmaceutical Research (1999), 16(5), 625-632
CODEN: PHREEB; ISSN: 0724-8741
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB Objectives of this study were (1) to further characterize cytochrome P 450 (CYP) and P-glycoprotein (Pgp) expression in monolayers of the Caco-2 cell clone TC7, a cell culture model of the human intestinal epithelium, and (2) to study the interplay between CYP3A and Pgp as barriers to intestinal drug absorption in TC7 cells using terfenadine and its metabolites as substrates. MRNA expression of eight CYPs and Pgp was investigated in TC7 and parental Caco-2 (Caco-2p) cell monolayers using RT-PCR. The CYP3A kinetics was determined in microsomes from both cell lines. The transport, metabolism and efflux of terfenadine and its metabolites were investigated in TC7 monolayers. Both TC7 and Caco-2p cells expressed mRNA for Pgp and several important CYPs. However, mRNA for CYP3A4 was detectable only from TC7 cells. The relative affinity of CYP3A for terfenadine metabolism in the two cell lines was comparable, but the maximum reaction rate in the TC7 cells was 8-fold higher. The rate of transport of terfenadine and its metabolites hydroxyterfenadine (HO-T) and azacyclonol across TC7 monolayers was 7.1-, 3.5- and 2.1-fold higher, resp., in the basolateral to apical direction than it was in the apical to basolateral (AP-BL) direction. Inhibition studies indicated that the efflux was mediated by Pgp. Ketoconazole increased the AP-BL transport of terfenadine dramatically by inhibiting both terfenadine metabolism and Pgp efflux. Cell culture models such as TC7 provide qual. information on drug interactions involving intestinal CYP3A and Pgp.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1999:231505 CAPLUS
DN 130:272005
TI Compositions and methods for treating respiratory disorders using naproxen and cetirizine
IN Mitra, Sekhar
PA The Procter & Gamble Company, USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9915173	A1	19990401	WO 1998-IB1339	19980828
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2304005	A1	19990401	CA 1998-2304005	19980828
	AU 9887443	A	19990412	AU 1998-87443	19980828
	EP 1014983	A1	20000705	EP 1998-938852	19980828
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	BR 9812660	A	20000822	BR 1998-12660	19980828
	HU 2000004813	A2	20010828	HU 2000-4813	19980828
	JP 2001517626	T	20011009	JP 2000-512542	19980828
PRAI	US 1997-934033	A	19970919		
	WO 1998-IB1339	W	19980828		

AB The present invention relates to compns. and methods for providing improved treatment, management or mitigation of cold, cold-like, allergy, sinus and/or flu symptoms by administering a safe and effective amount of a composition comprising naproxen along with cetirizine. E.g., a hard compressed tablet composition was prepared by combining naproxen sodium 220-440, cetirizine 5, microcryst. cellulose 110, povidone 10, talc 12, Mg stearate 2 and Opadry clear/Colorcon (containing HPMC) 5.0 mg, resp. Oral administration of tablets every 12 h to human in need of treatment provides improved relief from cough, cold-like, flu, flu-like and allergic rhinitis symptoms.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1998:635112 CAPLUS
DN 129:339442
OREF 129:68997a,69000a
TI Interaction of terfenadine and its primary metabolites with cytochrome P450 2D6
AU Jones, Barry C.; Hyland, Ruth; Ackland, Mark; Tyman, Christine A.; Smith, Dennis A.
CS Department of Drug Metabolism, Pfizer Central Research, Kent, CT13 9NJ, UK
SO Drug Metabolism and Disposition (1998), 26(9), 875-882
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
AB The substrate structure-activity relationships described for the major human drug-metabolizing cytochrome P 450 (P 450 or CYP) enzymes suggest that the H1 receptor antagonist terfenadine could interact with CYP2D6 either as a substrate or as an inhibitor, in addition to its known ability to act as a substrate for CYP3A4. Based on this substrate structure-activity relationship, computer modeling studies were undertaken to explore the likely interactions of terfenadine with CYP2D6. An overlay of terfenadine and dextromethorphan, a known substrate of CYP2D6, showed that it was possible to superimpose the site of hydroxylation (t-Bu group) and the nitrogen atom of terfenadine with similar regions in dextromethorphan. These observations were substantiated by the ease of docking of

terfenadine into a protein model of CYP2D6. Exptl., terfenadine inhibited CYP2D6 activity in human liver microsomes with an IC50 of 14-27 μM, depending on the CYP2D6 substrate used. The inhibition of CYP2D6 was further defined by determining the Ki for terfenadine against bufuralol 1'-hydroxylase activity in four human livers. Terfenadine inhibited bufuralol 1'-hydroxylase activity with a Ki of approx. 3.6 μM. The formation of the hydroxylated metabolite (hydroxyterfenadine) in microsomes prepared from human liver and specific P 450 cDNA-transfected B lymphoblastoid cells indicated that only CYP2D6 and CYP3A4 were involved in this transformation. As expected, the rate of formation was greatest with CYP3A4 (Vmax = 1257 pmol/min/nmol of P 450), with CYP2D6 forming the metabolite at a 6-fold lower rate (Vmax = 206 pmol/min/nmol of P 450). The two enzymes had similar KM values (9 and 13 μM, resp.). These data indicate that, as predicted from modeling studies, terfenadine has the structural features necessary for interaction with CYP2D6.

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1998:225593 CAPLUS
DN 129:114
OREF 129:23a,26a
TI Metabolism of epinastine, a histamine H1 receptor antagonist, in human liver microsomes in comparison with that of terfenadine
AU Kishimoto, Wataru; Hiroi, Toyoko; Sakai, Kenji; Funae, Yoshihiko; Igarashi, Takashi
CS Kawanishi Pharma Research Institute, Department of Drug Metabolism and Pharmacokinetics, Nippon Boehringer Ingelheim Co., Hyogo, 666-01, Japan
SO Research Communications in Molecular Pathology and Pharmacology (1997), 98(3), 273-292
CODEN: RCMPE6; ISSN: 1078-0297
PB PJD Publications Ltd.
DT Journal
LA English
AB Epinastine is a non-sedative second-generation antiallergic drug, like terfenadine. In the present study, the metabolism of epinastine in human liver microsomes was investigated and compared with that of terfenadine. Terfenadine was extensively metabolized to terfenadine acid with a Km value of 1.78 μM, a Vmax value of 173.8 pmol/min/mg and a metabolic clearance (Vmax/Km) of 103.9. Epinastine, in contrast, was poorly metabolized by microsomes from the same source with a high Km value of 232 μM. Metabolic clearance of epinastine was only 0.832, which was lower by three orders of magnitude than that of terfenadine. Studies with microsomes expressing recombinant cytochrome P 450 (CYP) species revealed that the CYP isoforms responsible for epinastine metabolism are CYP3A4, 2D6 and (to a minor extent) 2B6. Epinastine and terfenadine had no effect on CYP1A2 (theophylline 1-demethylation), 2C8/9 (tolbutamide hydroxylation) or 2E1 (chlorzoxazone 6-hydroxylation) activity, but weakly inhibited CYP2D6 (debrisoquine 4-hydroxylation) activity. CYP3A4 (testosterone 6β-hydroxylation) activity was strongly inhibited by terfenadine with a Ki value of 25 μM, whereas epinastine had no effect at ≤100 μM. Thus, epinastine is very poorly metabolized compared to terfenadine in human liver microsomes and does not inhibit CYP3A4 activity in vitro, unlike terfenadine.

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1997:573068 CAPLUS
DN 127:260640
OREF 127:50861a

TI Comparison of CYP3A activities in a subclone of Caco-2 cells (TC7) and human intestine
AU Raeissi, Shamsi D.; Guo, Zuyu; Dobson, Glenn L.; Artursson, Per; Hidalgo, Ismael J.
CS Drug Metabolism and Pharmacokinetics, Rhone-Poulenc Rorer Central Research, Collegeville, PA, 19426-0107, USA
SO Pharmaceutical Research (1997), 14(8), 1019-1025
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum
DT Journal
LA English
AB To compare the activity of the CYP3A enzyme expressed by TC7, a cell culture model of the intestinal epithelial cell, to the activity of human intestinal CYP3A4, using terfenadine as a substrate. The metabolism of terfenadine was investigated in intact cells and microsomal prepns. from TC7, human intestine, and liver. The effect of two CYP3A inhibitors, ketoconazole and troleandomycin (TAO), on the metabolism of terfenadine was also examined Only hydroxy-terfenadine was detected in TC7 microsomal incubations. In contrast, azacyclonol and hydroxy-terfenadine were detected in human intestinal and hepatic microsomal incubations. The Km values for hydroxy-terfenadine formation in TC7 cells, intestine and liver microsomes were 1.91, 2.5, and 1.8, μM resp. The corresponding Vmax values were 2.11, 61.0, and 370 pmol/min/mg protein. Km values for azacyclonol in intestinal and hepatic samples were 1.44 and 0.82 μM and the corresponding Vmax values were 14 and 60 pmol/min/mg protein. The formation of hydroxy-terfenadine was inhibited by ketoconazole and TAO in human intestine and TC7 cell microsomes. The Km and Vmax values for terfenadine metabolism in intact TC7 cells were similar to those from TC7 cell microsomes. Our results indicate that TC7 cells are a potentially useful alternative model for studies of CYP3A mediated drug metabolism The CYP3A expressed by TC7 cells is not CYP3A4, but probably CYP3A5, making this cell line suitable for studies of colonic drug transport and metabolism
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1997:153263 CAPLUS
DN 126:233059
OREF 126:44917a,44920a
TI Evaluation of drug interactions in intact hepatocytes: inhibitors of terfenadine metabolism
AU Jurima-Romet, M.; Huang, H. S.; Beck, D. J.; Li, A. P.
CS Bureau of Drug Research, Drugs Directorate, Health Protection Branch, Health Canada, Banting Research Centre 2201C, Ottawa, K1A 0L2, Can.
SO Toxicology in Vitro (1996), 10(6), 655-663
CODEN: TIVIEQ; ISSN: 0887-2333
PB Elsevier
DT Journal
LA English
AB Terfenadine has been associated with several adverse drug interactions and it was of interest to develop in vitro systems to explain and predict such interactions. The metabolism of terfenadine was studied using intact hepatocytes from primary human and rat hepatocyte cultures, and the immortalized human hepatoma cell line HepG2. Rates and routes of biotransformation were analyzed by HPLC. Terfenadine was extensively metabolized by all three cell culture systems during exposure periods ranging from 4 to 24 h. Human and rat hepatocytes and HepG2 cells formed products of C-oxidation (an acid metabolite and its precursor alc. metabolite). Human hepatocytes also formed the N-dealkylation product azacyclonol. Several cytochrome P 4503A (CYP3A) substrates and inhibitors were evaluated for their ability to inhibit terfenadine biotransformation.

In rat hepatocytes, ketoconazole, erythromycin and troleandomycin failed to inhibit; in HepG2 cells, only ketoconazole potently inhibited terfenadine metabolism In human hepatocytes, ketoconazole, itraconazole, erythromycin, troleandomycin, cyclosporin and naringenin inhibited terfenadine metabolism The results suggest that human hepatocytes may be a useful system for screening for inhibitors of terfenadine metabolism

L12 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1995:639962 CAPLUS
DN 123:74140
OREF 123:12875a,12878a
TI Metabolism of terfenadine associated with CYP3A(4) activity in human hepatic microsomes
AU Ling, Kah-Hiing J.; Leeson, Gerald A.; Burmaster, Steve D.; Hook, Robert H.; Reith, M. Kelly; Cheng, Lawrence K.
CS Dep. of Clinical Biotransformation, Marion merrell Dow, Inc., MO, USA
SO Drug Metabolism and Disposition (1995), 23(6), 631-6
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
AB Terfenadine (Seldane) undergoes extensive metabolism to form azacyclonol and terfenadine alc. Terfenadine alc. is subsequently metabolized to azacyclonol and terfenadine acid. Although testosterone 6β-hydroxylation [CYP3A(4)] has been shown to be the principal enzyme involved in the first step in terfenadine's biotransformation (formation of azacyclonol and terfenadine alc.), the enzymes catalyzing the subsequent metabolic steps in the conversion of terfenadine alc. to azacyclonol and terfenadine acid have not been identified. The purpose of these studies was to determine the role of cytochrome P 450 isoforms in the biotransformation of terfenadine and terfenadine alc. To this end, both terfenadine and its alc. were incubated with 10 individual human liver microsomal samples that have been characterized for major isoenzyme activities. The metabolites and parent drugs were quantified by HPLC. The formation of azacyclonol and terfenadine alc. from terfenadine is confirmed to be catalyzed predominantly by CYP3A(4) isoenzyme, and the ratio of the rate of terfenadine alc. formation to that o azacyclonol is 3:1. Involvement of the CYP3A(4) in terfenadine metabolism was further confirmed by the following studies: (a) inhibition of terfenadine alc. formation by ketoconazole and troleandomycin, two specific inhibitors of CYP3A(4), and (b) time course of terfenadine alc. formation by cloned human CYP3A(4). When terfenadine alc. was used as substrate, both the terfenadine acid and azacyclonol formation were also catalyzed by CYP3A(4) isoenzyme. However, the rate of formation of the terfenadine acid metabolite is almost 9 times faster than that of azacyclonol. The net ratio of terfenadine acid to azacyclonol is 2:1.

L12 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1995:431322 CAPLUS
DN 122:204587
OREF 122:37069a,37072a
TI In vitro prediction of the terfenadine-ketoconazole pharmacokinetic interaction
AU Moltke, Lisa L. Von; Greenblatt, David J.; Duan, Su Xiang; Harmatz, Jerold S.; Shader, Richard I.
CS Department Pharmacology and Experimental Therapeutics, Tufts University School Medicine, Boston, MA, 02111, USA
SO Journal of Clinical Pharmacology (1994), 34(12), 1222-7
CODEN: JCPCBR; ISSN: 0091-2700
DT Journal
LA English

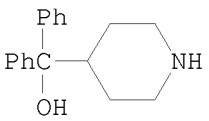
AB Biotransformation of the peripherally acting H-1 histamine antagonist, terfenadine, to its desalkyl and hydroxy metabolites was studied in vitro using microsomal prepns. from six sep. human livers. These metabolic reactions are mediated by the specific cytochrome P 450-3A4. Addition of ketoconazole to the reaction mixts. reduced the rate of formation of both metabolites in a manner consistent with competitive inhibition. Ketoconazole inhibition consts. (Ki) averaged 0.024 μM for the desalkyl terfenadine pathway, and 0.237 μM for the hydroxy terfenadine pathway. A math. model, based on the in vitro Ki values and the usual clin. range of plasma ketoconazole concns. (1-5 μg/mL; 1.88 - 0.94 μM), predicted that plasma terfenadine levels during coadministration of ketoconazole would increase by a factor ranging from 13-fold to 59-fold relative to the same dose of terfenadine given without ketoconazole. Actual plasma terfenadine levels during terfenadine-ketoconazole coadministration in a clin. pharmacokinetic study were close to those predicted by the model. These plasma levels were associated with prolongation of the corrected QT interval, thereby explaining the potentially life-threatening ventricular arrhythmias reportedly associated with terfenadine-ketoconazole cotherapy. Thus, data from studies of drug metabolism in vitro can be used to predict and thereby possibly avoid clin. important drug interactions.

L12 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1995:254554 CAPLUS
DN 122:23187
OREF 122:4389a,4392a
TI Terfenadine metabolism in human liver. In vitro inhibition by macrolide antibiotics and azole antifungals
AU Jurima-Romet, Malle; Crawford, Kim; Cyr, Terry; Inaba, Tadanobu
CS Bur. Drug Res., Health Canada, Ottawa, ON, K1A 0L2, Can.
SO Drug Metabolism and Disposition (1994), 22(6), 849-57
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
AB To determine whether the clin. adverse interactions of terfenadine with azole antifungals and macrolide antibiotics may be related to inhibition of terfenadine biotransformation, an in vitro system was developed to follow the metabolism of terfenadine by rat liver S9 or human liver microsomes. When test compds. were coincubated with terfenadine, the metabolites formed and unchanged terfenadine was quant. analyzed by HPLC. Five metabolites of terfenadine were formed by rat liver S9: predominantly alc. metabolite, with four minor metabolites - azacyclonol, acid metabolite, an unidentified metabolite, and a new ketone metabolite. By human liver microsomes, two major metabolites were formed: azacyclonol and alc. metabolite. Ketoconazole, fluconazole, itraconazole, erythromycin, clarithromycin, and troleandomycin potently inhibited terfenadine metabolism by human liver (IC50 = 4-10 μM), but inhibition by rat liver was weaker (IC50 = 87-218 μM) and 18% maximally for troleandomycin. Other CYP3A substrates (cyclosporin A, naringenin, and midazolam) also demonstrated potent inhibition of terfenadine biotransformation in human liver microsomes (IC50 = 17-24 μM). Substrates of other P 450 families [sparteine (CYP2D6), caffeine (CYP1A), and diclofenac (CYP2C)] only very weakly inhibited terfenadine metabolism Dixon plot analyses for human liver revealed competitive/reversible inhibition by the azole antifungals and macrolide antibiotics of azacyclonol and alc. metabolite formations. Cyclosporin A and naringenin competitively/reversibly inhibited only alc. metabolite formation, and midazolam, only azacyclonol formation, suggesting a heterogeneity of CYP3A4. In conclusion, azole antifungals, macrolide antibiotics, and other CYP3A substrates are capable of inhibiting the metabolism of terfenadine at therapeutically relevant concns.

CYP3A substrates include a large number of therapeutically important drugs. The potential of these substrates to interact with terfenadine should be evaluated in vivo.

L12 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1994:95096 CAPLUS
DN 120:95096
OREF 120:16691a,16694a
TI Effects of terfenadine and its metabolites on a delayed rectifier K+ channel cloned from human heart
AU Rampe, David; Wible, Barbara; Brown, Arthur M.; Dage, Richard C.
CS Marion Merrell Dow Res. Inst., Cincinnati, OH, 45215, USA
SO Molecular Pharmacology (1993), 44(6), 1240-5
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB Use of the nonsedating antihistamine terfenadine has been associated with altered cardiac repolarization in certain clin. settings. For this reason the authors examined the effects of terfenadine, and its metabolites, on a rapidly activating delayed rectifier K+ channel (fHK) cloned from human heart,. FHK was stably expressed in human embryonic kidney cells, and both whole-cell current and currents from excised inside-out patches were recorded. Terfenadine (3 μM) blocked whole-cell fHK current by 72 ± 6%. In inside-out patches, terfenadine applied to the cytoplasmic surface blocked fHK with an IC50 value of 367 nM. The main effect of terfenadine was to enhance the rate of inactivation of fHK current and thereby reduce the current at the end of a prolonged voltage-clamp pulse. The blockade displayed a weak voltage dependence, increasing at more pos. potentials. The mechanism of action of terfenadine is therefore consistent with blockade of open channels. In contrast, the metabolites of terfenadine were weakly active on fHK. IC50 values for all of the metabolites tested ranged from 27-fold to 583-fold higher than that obtained for terfenadine. It is concluded that terfenadine, but not its metabolites, blocks at least one type of human cardiac K+ channel at clin. relevant concns. and that this activity may underlie the cardiac arrhythmias that have been associated with the use of this drug.

L12 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1993:530854 CAPLUS
DN 119:130854
OREF 119:23241a,23244a
TI Oxidation of the antihistaminic drug terfenadine in human liver microsomes: role of cytochrome P-450 3A(4) in N-dealkylation and C-hydroxylation
AU Yun, Chul Ho; Okerholm, Richard A.; Guengerich, F. Peter
CS Sch. Med., Vanderbilt Univ., Nashville, TN, 37232-0146, USA
SO Drug Metabolism and Disposition (1993), 21(3), 403-9
CODEN: DMDSAI; ISSN: 0090-9556
DT Journal
LA English
GI



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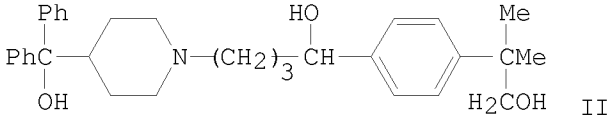

II

AB The antihistaminic drug terfenadine is of interest because of its lack of

sedative properties. Major routes of metabolism include oxidative N-dealkylation to 4-(hydroxydiphenylmethyl)piperidine (I) and oxidation of a tert-Bu Me group to a primary alc. (II), which is subsequently oxidized to a carboxylic acid. Rates of formation of I and II varied .apprx.30-fold in the 17 human liver microsomal samples examined and were highly correlated with each other, suggesting that the same enzyme may be involved in both oxidns. The rates of formation of I and II were both correlated with rates of nifedipine oxidation [a marker of cytochrome P 450 (P 450) 3A4] but not with markers for other human P-450s. Microsomal oxidation of both enantiomers of terfenadine to I and II was markedly inhibited by gestodene, a selective mechanism-based inactivator of P 450 3A enzymes but not by any of several other P 450 inhibitors. Antibodies raised against P 450 3A4 could inhibit most of the oxidation of (both enantiomers) terfenadine to I and II in a microsomal sample having high catalytic activity but antibodies recognizing other P-450s had no effect. The oxidation of terfenadine to I and II was catalyzed by purified human liver microsomal P 450 3A4 and by partially purified yeast recombinant P 450 3A4. These results provide evidence that P 450 3A4 (and possibly other P 450 3A enzymes) play a major role in the oxidation of (both enantiomers) terfenadine to both of its major oxidation products. Further factors known to modulate P 450 3A4 activity can be considered for their effects on the disposition of tefenadine, but it does not appear that genetic polymorphism should be involved in the disposition of this drug.

L12 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1992:419768 CAPLUS
DN 117:19768
OREF 117:3381a,3384a
TI Determination of the metabolites of terfenadine in human urine by thermospray liquid chromatography-mass spectrometry
AU Chen, T. M.; Chan, K. Y.; Coutant, J. E.; Okerholm, R. A.
CS Marion Merrel Dow Res. Inst., Cincinnati, OH, 45215-6300, USA
SO Journal of Pharmaceutical and Biomedical Analysis (1991), 9(10-12), 929-33
CODEN: JPBADA; ISSN: 0731-7085
DT Journal
LA English
AB Thermospray liquid chromatog.-mass spectrometry (TSP LC-MS) was used to determine
human urinary metabolites of terfenadine after oral administration of terfenadine tablets. In addition to the two previously identified major metabolites, azacyclonol (MDL 4829) and the acid metabolite (MDL 16,455), three addnl. metabolites were also detected. One of the addnl. metabolites was identified as the alc. metabolite (MDL 17,523) and the other two were proposed to be an aldehyde and a ketone-acid from their TSP mass spectra. The results of this study demonstrate that TSP LC-MS is a useful technique for the study of terfenadine biotransformation.

L12 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1981:156758 CAPLUS
DN 94:156758
OREF 94:25625a,25628a
TI Piperidine derivatives with antihistamine action
IN Carr, Albert A.; Dolfini, Joseph E.; Wright, George J.
PA Richardson-Merrell Inc., USA
SO Ger. Offen., 39 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	DE 3007498	A1	19801023	DE 1980-3007498	19800228
	DE 3007498	C2	19890907		
	US 4254129	A	19810303	US 1979-28813	19790410
	CA 1123438	A1	19820511	CA 1980-344020	19800118
	IL 59158	A	19840430	IL 1980-59158	19800118
	ZA 8000332	A	19810128	ZA 1980-332	19800121
	AU 8055016	A	19801016	AU 1980-55016	19800129
	AU 531146	B2	19830811		
	NL 8000754	A	19801014	NL 1980-754	19800207
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	NL 190580	C	19940502		
	CH 643245	A5	19840530	CH 1980-1741	19800305
	AT 8001448	A	19840315	AT 1980-1448	19800317
	AT 376208	B	19841025		
	DK 8001329	A	19801011	DK 1980-1329	19800327
	DK 153709	B	19880822		
	DK 153709	C	19881227		
	GB 2048258	A	19801210	GB 1980-10997	19800402
	GB 2048258	B	19830330		
	SE 8002634	A	19801011	SE 1980-2634	19800408
	SE 448726	B	19870316		
	SE 448726	C	19870625		
	BE 882703	A1	19800731	BE 1980-200161	19800409
	NO 8001014	A	19801013	NO 1980-1014	19800409
	NO 154521	B	19860630		
	NO 154521	C	19861008		
	JP 55141469	A	19801105	JP 1980-45771	19800409
	JP 01032823	B	19890710		
	FR 2453854	A1	19801107	FR 1980-7992	19800409
	FR 2453854	B1	19830624		
	US 4285957	A	19810825	US 1980-196505	19801014
PRAI	US 1979-28813	A	19790410		
	US 1979-28872	A	19790410		

OS CASREACT 94:156758; MARPAT 94:156758

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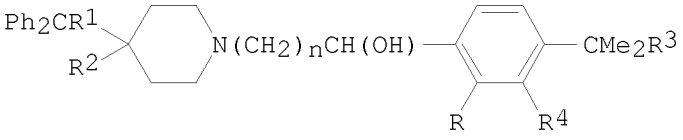
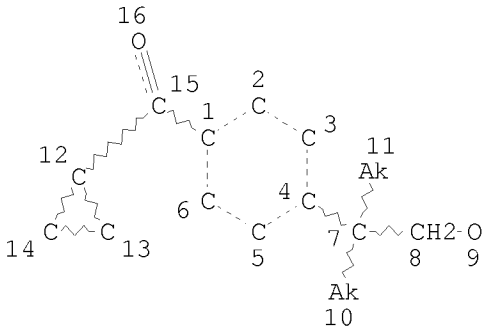


I

AB The title compds. [I; R, R1, R4 = H, OH; R2 = H; R1R2 = bond; R3 = Me, CH2OH, (esterified) CO2H; n = 1-5] and their salts were prepared for use as antihistaminics, antiallergics, and bronchodilators (no data). Thus, Cl(CH2)3COCl was treated with PhCMe2CO2Et in the presence of AlCl3, and the product treated with α,α-diphenyl-4-piperidinemethanol, followed by catalytic reduction to give I (R = R2 = R4 = H, R1 = OH, R3 = CO2Et, n = 3).

=> d l13
L13 HAS NO ANSWERS
L13 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1 12
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE

=> d his l15

(FILE 'REGISTRY' ENTERED AT 08:51:05 ON 28 OCT 2008)
L15 2 S L13 FUL

=> d bib abs 1-4 l16

L16 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:534160 CAPLUS
DN 141:88921
TI Process for the preparation of an intermediate in the manufacture of fexofenadine
IN Sharma, Mukesh Kumar; Khanduri, Chandra Has; Kumar, Naresh
PA Ranbaxy Laboratories Limited, India
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004054955	A1	20040701	WO 2003-IB5994	20031215
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2510158	A1	20040701	CA 2003-2510158	20031215
AU 2003286352	A1	20040709	AU 2003-286352	20031215
EP 1575893	A1	20050921	EP 2003-777096	20031215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

	BR 2003017364	A	20051116	BR 2003-17364	20031215
	CN 1741981	A	20060301	CN 2003-80109094	20031215
	US 20060173042	A1	20060803	US 2005-538956	20050614
PRAI	IN 2002-DE1262	A	20021216		
	WO 2003-IB5994	W	20031215		

OS CASREACT 141:88921

AB 2-[4-[Cyclopropyl(carbonyl)]phenyl]-2-methyl-2-propanoic acid, an intermediate for the preparation of the antihistamine fexofenadine, is prepared by the addition of an alkali (e.g., sodium hydroxide) to the corresponding alc. [e.g., 2-[4-[cyclopropyl(carbonyl)]phenyl]-2-methyl-2-propanol], followed by addition of an aqueous oxidant (e.g., aqueous potassium permanganate solution), and an acidic (e.g., hydrochloric acid) workup.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2003:5929 CAPLUS

DN 138:73082

TI Preparation of 4-(cyclopropylcarbonyl)-α,α-dimethylphenylacetic acid

IN Ramesh, Dandala; Umashankar, Das; Divvela, Venkata Naga Srinivasa Rao; Meenakshi, Sunderam Sivakumaran

PA Aurobindo Pharma Limited, India

SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003000658	A1	20030103	WO 2002-IN135	20020619
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	IN 193428	A1	20040717	IN 2001-MA511	20010625
	AU 2002317469	A1	20030108	AU 2002-317469	20020619
	SI 21232	A	20031231	SI 2002-20003	20020619
	EP 1401815	A1	20040331	EP 2002-745778	20020619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004521942	T	20040722	JP 2003-507065	20020619
	BG 107476	A	20040130	BG 2003-107476	20030117
	US 20040077900	A1	20040422	US 2003-612637	20030702
	US 6903232	B2	20050607		
PRAI	IN 2001-MA511	A	20010625		
	WO 2002-IN135	W	20020619		

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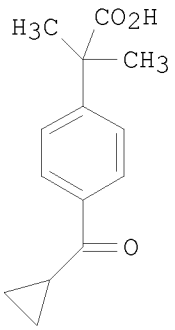

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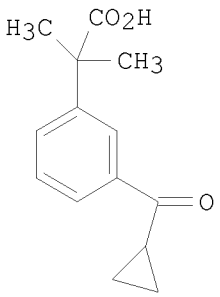

II

AB A process to obtain highly pure 4-(cyclopropylcarbonyl)-α,α-dimethylphenylacetic acid (I) through crystallization from a mixture of para and meta regioisomers of I and 3-(cyclopropylcarbonyl)-α,α-dimethylphenylacetic acid (II) in cyclohexane, whereby the amount of undesired meta isomer II is decreased to below 0.5%, is described. Compound I is converted in the invention to highly pure terfenadine carboxylate, which is a known antihistaminic (no data).

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:408068 CAPLUS
DN 135:19556
TI Preparation of [(piperidinoalkanoyl)phenyl]propionates and analogs as antihistaminics
IN Krauss, Richard C.; Strom, Robert M.; Scortichini, Carey L.; Kruper, William J.; Wolf, Richard A.; Wu, Weishi W.; Carr, Albert A.; Hay, David A.; Rudisill, Duane E.; Panzone, Gianbattista
PA Merrell Pharmaceuticals Inc., USA
SO U.S., 60 pp., Cont.-in-part of U.S. Ser. No. 237,466.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6242606	B1	20010605	US 1994-275685	19940714
	CA 2166059	A1	19950105	CA 1994-2166059	19940526
	CA 2166059	C	20050816		
	CA 2362337	C	19950105	CA 1994-2362337	19940526
	CA 2362337	A1	19950105		
	CA 2362339	C	19950105	CA 1994-2362339	19940526
	CA 2362339	A1	19950105		
	CN 1128987	A	19960814	CN 1994-193031	19940526
	EP 1260504	A1	20021127	EP 2002-12626	19940526
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	ES 2190442	T3	20030801	ES 1994-919264	19940526
	CN 1603291	A	20050406	CN 2004-10058716	19940526
	CN 1275916	C	20060920		
	EP 1953142	A1	20080806	EP 2008-8300	19940526
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	ZA 9404380	A	19950209	ZA 1994-4380	19940620
	IL 110086	A	20010913	IL 1994-110086	19940622
	IL 143607	A	20050725	IL 1994-143607	19940622
	IL 143613	A	20050725	IL 1994-143613	19940622

	IL 143619	A	20050831	IL 1994-143619	19940622
	US 6147216	A	20001114	US 1995-458747	19950602
	AU 9915458	A	19990624	AU 1999-15458	19990208
	AU 734870	B2	20010621		
	CN 1274711	A	20001129	CN 2000-101035	20000112
	US 20010018521	A1	20010830	US 2000-725291	20001129
	US 6566526	B2	20030520		
	US 20010020114	A1	20010906	US 2000-725259	20001129
	US 6552200	B2	20030422		
	US 6340761	B1	20020122	US 2000-725298	20001129
	US 20010000038	A1	20010315	US 2000-726625	20001201
	US 6479663	B2	20021112		
	US 20020198407	A1	20021226	US 2000-726580	20001201
	US 6555689	B2	20030429		
	US 20020007085	A1	20020117	US 2000-729203	20001205
	US 6548675	B2	20030415		
	US 20010021791	A1	20010913	US 2000-731654	20001208
	US 6559312	B2	20030506		
	US 20020077482	A1	20020620	US 2001-818966	20010328
	US 6441179	B2	20020827		
	US 20010031895	A1	20011018	US 2001-824788	20010404
	US 6348597	B2	20020219		
	HK 1032226	A1	20041231	HK 2001-102808	20010420
	MX 2001PA07687	A	20030303	MX 2001-PA7687	20010730
	MX 2001PA07688	A	20030303	MX 2001-PA7688	20010730
	MX 2001PA07692	A	20030303	MX 2001-PA7692	20010730
	MX 2001PA07693	A	20030303	MX 2001-PA7693	20010730
	US 20030220496	A1	20031127	US 2003-364641	20030212
	US 6777555	B2	20040817		
	JP 2005320329	A	20051117	JP 2005-133801	20050502
	HK 1075884	A1	20070511	HK 2005-107826	20050907
PRAI	US 1993-82693	B2	19930625		
	US 1993-144084	A2	19931027		
	US 1994-237466	A2	19940511		
	AU 1994-70466	A3	19940526		
	CA 1994-2166059	A3	19940526		
	EP 1994-919264	A3	19940526		
	EP 2002-12626	A3	19940526		
	JP 1995-502831	A3	19940526		
	IL 1994-110086	A	19940622		
	US 1994-275685	A1	19940714		
	US 2000-725259	A3	20001129		

OS MARPAT 135:19556

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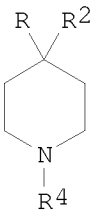

I

AB Title compds. [I; R = R1CPh2Om; R1 = H or OH; R2 = H; R1R2 = bond; R4 = (CH2)nZZ1CMe2R3; R3 = CO2H or alkoxycarbonyl; Z = CO or CH(OH); Z1 = (2-hydroxy) 1,4-phenylene; m = 0 or 1; N = 1-5] were prepared as antihistaminics (no data). Thus, PhCMe2CO2Me was acylated by Cl(CH2)3COCl

and the product aminated by α,α-diphenyl-4-piperidinemethanol to give I.HCl [R = HOCPh2, R2 = H, R4 = (CH2)3COC6H4(CMe2CO2Me)-4].

RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1995:871983 CAPLUS
DN 123:285787
OREF 123:51211a,51214a
TI Preparation of [(hydroxybenzhydryl)piperidinoalkanoyl]phenylalkanoates and analogs as antihistaminics
IN Krauss, Richard C.; Strom, Robert M.; Scortichini, Carey L.; Kruper, William J.; Wolf, Richard A.; Carr, Albert A.; Rudisill, Duane E.; Panzone, Gianbattista; Hay, David A.; Wu, Weishi W.
PA Merrell Dow Pharmaceuticals Inc., USA
SO PCT Int. Appl., 236 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9500480	A1	19950105	WO 1994-US5982	19940526
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2166059	A1	19950105	CA 1994-2166059	19940526
CA 2166059	C	20050816		
CA 2362337	C	19950105	CA 1994-2362337	19940526
CA 2362337	A1	19950105		
CA 2362339	C	19950105	CA 1994-2362339	19940526
CA 2362339	A1	19950105		
AU 9470466	A	19950117	AU 1994-70466	19940526
AU 699559	B2	19981210		
EP 705245	A1	19960410	EP 1994-919264	19940526
EP 705245	B1	20030102		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1128987	A	19960814	CN 1994-193031	19940526
HU 74092	A2	19961128	HU 1995-3705	19940526
HU 226037	B1	20080328		
JP 08512028	T	19961217	JP 1995-502831	19940526
JP 3712208	B2	20051102		
EP 1260504	A1	20021127	EP 2002-12626	19940526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 230395	T	20030115	AT 1994-919264	19940526
ES 2190442	T3	20030801	ES 1994-919264	19940526
CN 1603291	A	20050406	CN 2004-10058716	19940526
CN 1275916	C	20060920		
EP 1953142	A1	20080806	EP 2008-8300	19940526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
ZA 9404380	A	19950209	ZA 1994-4380	19940620
IL 110086	A	20010913	IL 1994-110086	19940622
IL 143607	A	20050725	IL 1994-143607	19940622
IL 143613	A	20050725	IL 1994-143613	19940622
IL 143619	A	20050831	IL 1994-143619	19940622
FI 9506248	A	19960219	FI 1995-6248	19951222
FI 114912	B1	20050131		
NO 9505255	A	19960226	NO 1995-5255	19951222
NO 313191	B1	20020826		

	AU 9915458	A	19990624	AU 1999-15458	19990208
	AU 734870	B2	20010621		
	CN 1274711	A	20001129	CN 2000-101035	20000112
	HK 1032226	A1	20041231	HK 2001-102808	20010420
	MX 2001PA07687	A	20030303	MX 2001-PA7687	20010730
	MX 2001PA07688	A	20030303	MX 2001-PA7688	20010730
	MX 2001PA07692	A	20030303	MX 2001-PA7692	20010730
	MX 2001PA07693	A	20030303	MX 2001-PA7693	20010730
	NO 2002002129	A	19960226	NO 2002-2129	20020503
	NO 319850	B1	20050919		
	FI 2003001381	A	20030925	FI 2003-1381	20030925
	NO 2003004811	A	19960226	NO 2003-4811	20031028
	JP 2005320329	A	20051117	JP 2005-133801	20050502
	HK 1075884	A1	20070511	HK 2005-107826	20050907
PRAI	US 1993-82693	A	19930625		
	US 1993-144084	A	19931027		
	US 1994-237466	A	19940511		
	AU 1994-70466	A3	19940526		
	CA 1994-2166059	A3	19940526		
	EP 1994-919264	A3	19940526		
	EP 2002-12626	A3	19940526		
	JP 1995-502831	A3	19940526		
	WO 1994-US5982	W	19940526		
	IL 1994-110086	A	19940622		

OS MARPAT 123:285787

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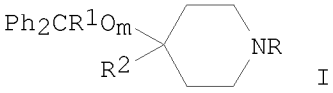

I

AB Title compds. I [R = (CH2)nWC6H3A(CMe2R3)-2,4; A, R1 = H or OH; R2 = H; R1R2 = bond; R3 = CO2H, alkoxycarbonyl, etc.; W = CO, CH(OH); m = 0 or 1; n = 1-5] were prepared as antihistaminics (no data). Thus, PhCMe2CO2Et was treated with Cl(CH2)3COCl and AlCl3 and the Ph cyclopropyl ketone product treated with HCl to give 4-[Cl(CH2)3CO]C6H4CMe2CO2Et which was condensed with azacyclonol to give I [R = (CH2)3COC6H4(CMe2CO2Et)-4, R1 = OH, R2 = H, m = 0].